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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/757,345	AGRAWAL ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-146* is/are pending in the application.

4a) Of the above claim(s) *2-30 and 32-146* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *Mar.11, 2004, July 22, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on November 14, 2006 is acknowledged.

Applicant has elected the invention of Group I, drawn to an immunomer compound comprising at least two oligonucleotides linked together. Claims 2, 4, 6, 17, 19-26, 28-30 and 32-146 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Within Group I, Applicant has elected the oligonucleotide linkage species to be "iv", a sugar to a non-nucleotide linker.

Within Group I, Applicant has elected the "G" moiety species to be "2'-deoxy-7-deazaguanosine".

The art is silent with respect the instantly elected embodiment of an immunomer compound comprising at least two oligonucleotides linked at their sugars to a non-nucleotidic linker, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure RpG, wherein the "R" moiety is 2-oxo-7-deaza-8-methyl-purine (also known in the art as [N,5-(1-methyl-1,2-ethenediyl)]cytosine) and the "G" moiety is 2'-deoxy-7-deazaguanosine", as of the effective priority date of the instant application is granted as January 16, 2003. As such, the species elections regarding the oligonucleotide linkage species and the "G" moiety species have been withdrawn because those species are free of the prior art.

2. Election of Applicant's invention(s) was made without traverse. Because applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

Amendments

3. Applicants' amendments to the claims in the reply filed November 14, 2006 is acknowledged. Applicant has withdrawn Claims 3, 5, 7-16 and 18 from examination of the Group I invention.

Applicant cancelled Claim 27 in the amendment filed October 1, 2004. Claims 2-26, 28-30 and 32-146 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

4. Claims 1 and 31 are under consideration.

Priority

5. Applicant's claim for the benefit of a prior-filed parent provisional application 60/440,587 filed on January 16, 2003 under 35 U.S.C. 119(e) is acknowledged. Accordingly, the effective priority date of the instant application is granted as January 16, 2003.

It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/440,587 filed on January 16, 2003. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the

national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Specification

6. The disclosure is objected to because of the following informalities:

A) The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless

the references have been cited by the examiner on form PTO-892, they have not been considered.

B) Applicant has amended the specification on April 19, 2004 so as to provide SEQ ID NO's to the numerous oligonucleotides disclosed in the numerous Tables. However, the column heading "CpG DNA Number" in Tables 16, 18 and 19 was not amended to "SEQ ID NO" so as to provide clear concordance between a particular CpG oligonucleotide, e.g. SEQ ID NO 153, and the effects a given oligonucleotide yields, e.g. spleen cell proliferation (Table 19). At present, the CpG DNAs are without antecedent basis in the disclosure, and there are no demonstrations of the immunological activity of the oligonucleotides identified by their respective SEQ ID NO. For the purpose of compact prosecution, the Examiner will interpret a direct concordance between "SEQ ID NO" and "CpG DNA Number"; however, appropriate correction is required.

C) The ATCC address is incorrect (pg 57, line 10). Applicant is reminded that the following and should amend the specification accordingly. The current address of the ATCC is as follows:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. **Claims 1 and 31 are provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 1-2 of copending Application No. 10/279,684.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunomers having at least two oligonucleotides linked together by a non-nucleotidic linker, wherein the internucleoside linkage is a phosphorothioate, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure RpG, wherein the "R" a non-natural pyrimidine nucleoside and wherein the "G" moiety is 2'-deoxy-7-deazaguanosine. The claims also recite a pharmaceutical composition comprising the inventive immunomer and a physiologically acceptable carrier. Thus, the composition(s) of the instant claim(s) is reasonably embraced by the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

8. **Claim 1 is provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claim 1 of copending Application No. 10/361,111.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunomers having at least two oligonucleotides linked together by a non-nucleotidic linker, wherein the internucleoside linkage is modified, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside. Thus, the composition(s) of the instant claim(s) is reasonably embraced by the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

9. **Claims 1 and 31 are provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 1, 11 and 16 of copending Application No. 11/153,054.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a non-natural purine nucleoside.

Because the claims of copending Application No. 11/153,054recite generically "CpG, C*pG, C*pG* and CpG*", the Examiner has looked to the specification for definitions of the "C" and "G" moieties so as to better understand the invention. The specification discloses that C* is... 1-(2'-deoxy-β-D-ribofuranosyl)-2-oxo-7-deaza-8-methyl-purine, and that G* is... 2'-deoxy-7-deazaguanosine (pg 1, [0010]), wherein the non-nucleotidic linker may be a 3'-3' linkage (pg 3, [0032]).

Thus, instantly claimed immunomer composition(s) anticipate immunostimulatory oligonucleotide(s) of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

10. **Claims 1 and 31 are provisionally rejected** on the ground of nonstatutory obviousness-type double patenting over Claims 1 and 4 of copending Application No. 11/174,002.

Although the conflicting claims are not identical, they are not patentably distinct from each other because they both claim immunostimulatory oligonucleotide compositions comprising an immunostimulatory dinucleotide having the structure of a non-natural pyrimidine nucleoside and a natural or non-natural purine nucleoside.

Thus, instantly claimed immunomer composition(s) anticipate immunostimulatory oligonucleotide(s) of the copending application.

This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. **Claims 1 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a vast genus of oligonucleotides and immunomers. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention.

Vas-cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116).

The claims are directed to a product, an immunomer, comprising at least two oligonucleotides linked together by a non-nucleotidic linker, wherein at least one of the oligonucleotides is an immunostimulatory oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide. The instantly elected invention is drawn to a composition comprising an immunostimulatory dinucleotide of formula 5'-Pur*-Pur-3', wherein Pur* is a non-natural purine nucleoside and Pur is a non-natural purine nucleoside (pg 5, lines 14-20), specifically the structure illustrated in Figure 24, wherein the "R" moiety has the structure known in the art (Kandimalla et al, PNAS 11(24): 14303-14308, 2003; Figure 1) as 2-oxo-7-deaza-8-methyl-purine, and the "G" moiety is 2'-deoxy-7-deazaguanosine".

With respect to the immunostimulatory dinucleotides of formula 5'-Pur*-Pur-3', the use of the term "has" recited in the claim is reasonably interpreted to embrace an enormous genus of immunostimulatory dinucleotides of formula 5'-Pur*-Pur-3', wherein Pur* represents an enormous genus of structurally diverse non-natural purine nucleosides all sharing the core structure of 2-oxo-7-deaza-8-methyl-purine, as illustrated. Nowhere in the instant specification is there a working example of the instantly elected invention, specifically an immunomer compound comprising at least two oligonucleotides linked at their sugars to a non-nucleotidic linker, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure RpG, wherein the "R" moiety is 2-oxo-7-deaza-8-methyl-purine and the "G" moiety is 2'-deoxy-7-deazaguanosine".

With respect to the at least two oligonucleotides that comprise the immunomer, the claims do not define the structure of the at least two oligonucleotides. The specification indicates only that an immunostimulatory oligonucleotide refers to an oligonucleotide that induces an

immune response when administered to a vertebrate, such as a fish, fowl, or mammal (pg 19, lines 10-13). Furthermore, the claims fail to define the structure and function of the oligonucleotide. The specification discloses that immunomers comprise at least one immunostimulatory dinucleotide comprising at least one modified purine or pyrimidine (pg 5, lines 11-13). The structure of the immunomer (at least two oligonucleotides) is vast in view of the recitation of the open claim language of "comprising", and is expanded even further by the enormous genus of contemplated chemically-modified purines and pyrimidines.

The recitation of "comprising" indicates that there are other structural components to the claimed oligonucleotides, immunostimulatory oligonucleotides and immunomers. The structures of the additional nucleic acids in the oligonucleotides and the immunomers are not known. The oligonucleotides and immunomers recited in the pending claimed genus would not clearly apprise one skilled in the art that the inventors had possession of the claimed genus and all species encompassed thereby as of the filing date. The structure of these oligonucleotides and immunomers has not been specifically defined. The claims recite that at least one of the oligonucleotides is an immunostimulatory oligonucleotide. However, the function of the other oligonucleotides is not known. The claims do not set forth the specific structure of the claimed oligonucleotides and immunomers and it is not clear if the claims or specification give the structure and a function of the oligonucleotide, as required by written description guidelines.

The structure of these immunomers has not been specifically defined and then shown that they each functions as an immunomer by stimulating the immune system. It is not clear if the claims give the structure and a function of the immunomer, as required by written description guidelines. It is noted that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. An adequate written description of a chemical invention also requires a precise definition, such

as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed.

A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559,1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); *In re Ruschig*, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967) ("If n-propylamine had been used in making the compound instead of n-butylamine, the compound of claim 13 would have resulted. Appellants submit to us, as they did to the board, an imaginary specific example patterned on specific example 6 by which the above butyl compound is made so that we can see what a simple change would have resulted in a specific supporting disclosure being present in the present specification. The trouble is that there is no such disclosure, easy though it is to imagine it.") (emphasis in original); *Purdue Pharma L.P.v. Faulding Inc.*, 230 F.3d 1320, 1328, 56 USPQ2d 1481, 1487 (Fed. Cir. 2000) ("the specification does not clearly disclose to the skilled artisan that the inventors ... considered the ratio.., to be part of their invention .... There is therefore no force to Purdue's argument that the written description requirement was satisfied because the disclosure revealed a broad invention from which the [later-filed] claims carved out a patentable portion").

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided: The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

The Revised Interim Guidelines state, "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. ...In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Further, *Vas-cath Inc. v.*

Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-cath* at page 1116). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that Claims 1 and 31 do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded

that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

12. **Claims 1 and 31 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claim is directed to a pharmaceutical composition comprising an immunomer and a physiologically acceptable carrier, wherein the instantly elected embodiment is an immunomer compound comprising at least two oligonucleotides linked at their sugars to a non-nucleotidic linker, wherein at least one of the oligonucleotides is an oligonucleotide having an accessible 5' end and comprising an immunostimulatory dinucleotide having the structure RpG, wherein the

"R" moiety is 2-oxo-7-deaza-8-methyl-purine and the "G" moiety is 2'-deoxy-7-deazaguanosine".

The claims are broad for encompassing an enormous genus of structurally diverse immunomer compositions comprising an enormous genus of structurally diverse oligonucleotides, wherein at least one oligonucleotide comprises an enormous genus of structurally diverse immunostimulatory dinucleotides.

The specification contemplates that the immunomer and compositions comprising the immunomer will be used for increasing the immunostimulatory effect of immunostimulatory oligonucleotide for immunotherapy applications (pg 5, line 5). "In a second aspect, the invention provides immunomer conjugates, comprising an immunomer, as described above, and an antigen conjugated to the immunomer at a position other than the accessible 5' end. In a third aspect, the invention provides pharmaceutical formulation comprising an immunomer or an immunomer conjugate according to the invention and a physiologically acceptable carrier. In a fourth aspect, the invention provides methods for generating an immune response in a vertebrate, such methods comprising administering to the vertebrate an immunomer or immunomer conjugate according to the invention. In some embodiments, the vertebrate is a mammal. In a fifth aspect the invention provided methods for therapeutically treating a patient having a disease or disorder, such methods comprising administering to the patient an immunomer or immunomer conjugate according to the invention. In various embodiments, the disease or disorder to be treated is cancer, an autoimmune disorder, airway inflammation, asthma, allergy, or a disease caused by a pathogen." (pgs 7-8)

"The invention provides methods for enhancing the immune response caused by immunostimulatory compounds used for immunotherapy applications such as, but not limited to, treatment of cancer, autoimmune disorders, asthma, respiratory allergies, food allergies, and bacteria, parasitic, and viral infections in adult and pediatric human and veterinary applications. Thus, the invention further provides compounds having optimal levels of immunostimulatory effect for immunotherapy and methods for making and using such compounds. In addition, immunomers of the invention are useful as adjuvants in combination with DNA vaccines, antibodies, allergens, chemotherapeutic agents, and antisense oligonucleotides." (pg 14, lines 8-

16) The specification indicates that vertebrate encompasses mammals, including humans (pg 19, line 14).

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The state of the art indicates (Applicants have set forth in the specification) that "... several researchers have demonstrated the validity of the use of oligonucleotides as immunostimulatory agents in immunotherapy applications. The observation that phosphodiester and phosphorothioate oligonucleotides can induce immune stimulation has created interest in developing this side effect as a therapeutic tool. These efforts have focused on phosphorothioate oligonucleotides containing the dinucleotide natural CpG. Kuramoto et al (Jpn. J. Cancer Res. 83:1128-1131, 1992; * of record, C11) teach that phosphodiester oligonucleotides containing a palindrome that includes a CpG dinucleotide can induce interferon-alpha and gamma synthesis and enhance natural killer activity. Krieg et al (Nature 371:546-549, 1995; * of record, C12) disclose that phosphorothioate CpG-containing oligonuclcotides are immunostimulatory. Liang et al (J. Clin. Invest. 98:1119-1129, 1996; * of record, C13) disclose that such oligonucleotides activate human B cells. Moldoveanu et al (Vaccine 16:1216-1224, 1998, * of record, C14) teach that CpG-containing phosphorothioate oligonucleotides enhance immune response against influenza virus. McCluskie and Davis (J. Immunol. 161:4463-4466, 1998; * of record, C15) teach that CpG-containing oligonucleotides act as potent adjuvants, enhancing immune response against hepatitis B surface antigen." (specification, pgs 3-4, joining ¶)

However, there has been very little research on the claimed immunomers, the second-generation immunostimulatory oligonucleotides. Kandimalla et al (Bioconjugate Chem. 13, 966-974, 2002; Nucleic Acid Research Vol. 31, No. 9, 2003; PNAS 100(24): 14303–14308, 2003) teach that preliminary *in vivo* experiments have been done that indicate the these immunomers prevented conalbumin-induced and ragweed-induced allergic inflammation in mice, and were effective in certain tumors. These minimal examples would not give one of ordinary skill in the art at the time the invention was made the necessary guidance to know that these immunomers could be successfully used in the treatment of the myriad and numerous diseases, disorders and conditions that Applicants have set forth in the specification. The successful treatment with one

tumor does not address if the immunomers will provide immunotherapeutic treatment for cancers such as lung cancers or breast cancers, for example. It is not clear whether any or all of the different possible structure variations for the immunomers, set forth in the specification, would be successful as a compound for treatment of animals or humans with viral or bacterial infections or diseases, cancers or allergies.

Further, the state of the art with regard to cancer therapy is unpredictable, in addition CpG immunostimulatory nucleic acid molecules in cancer therapy is unpredictable. Donnelly et al (Nature Medicine, 9(11):1354-1356, 2003) teach that over many decades various approaches to eliciting both innate and acquired immune responses against tumors have been tried, some with a degree of success. However, immunotherapy has yet to be incorporated into first-line therapies for more than a very few types of cancers such as the use of IL-2 immunotherapy for metastatic renal cell carcinoma (p. 1354, col. 2). Further, Donnelly et al teach that treating cancer with something that looks more like a modern-day vaccine, with a defined antigen and an optimized adjuvant and delivery platform, is still in the future (see p. 1354, col. 2; see also col. 3). "A variety of anti-tumor vaccine clinical trials have been undertaken. In spite of the large number of these trials, and the plethora of distinct approaches investigated, there has been little evidence of clinical efficacy. Furthermore, precise correlates of clinical effects and immunological responses have been lacking." (DeGruijl et al, Nature Medicine, 5110: 1124-1125, 1999; see p. 1124, col. 1) Bitton R. J. (Current Opinion in Molecular Therapeutics 611: 17-26, 2004; Abstract only) teaches that developing cancer vaccines to treat solid tumors is not an easy task (abstract). Bitton teaches that "immune editing", in part, explains why many cancer vaccines work in animal models but not in a clinical setting (abstract). Bitton describes the various cancer vaccine strategies and evaluates the evidence supporting their efficacy (abstract). Bitton indicates that the final picture with regard to cancer vaccines is confusing and comparison of different vaccine strategies is almost impossible because of the different strategies from different groups. Further, most of the vaccines are still experimental, far from being approved by regulatory authorities and their clinical utility is almost negligible (abstract). Bitton teaches that therapeutic vaccines have proved to have little use in cancer treatment and that in fact in almost every well-designed, well-controlled, randomized phase III trial, they have failed to demonstrate any significant improvement in overall or disease-free survival (p. 17, col. 2; Table 2). "It is clear

that most vaccines are indeed effective immunogens, but they do not seem to be effective at triggering anticancer responses. Tumor size reduction, the classic endpoint in clinical development of cytotoxic drugs does not seem to be useful in evaluating cancer vaccines; tumor stabilization might be more valuable. Finally, there is no evidence of improvement in overall survival or disease-free survival. The implementation of well-designed randomized phase III trials is urgently required." (pp. 24-25) This is just an example of the state of the art for cancer treatments.

With regard to CpG in the treatment of cancers, Weiner (J. Leukoc. Biol. 68: 455-463, 2000) indicates that there is therapeutic potential in cancer treatment for CpG as an immune adjuvant (Table 1) and that there are a number of scenarios where CpG could be used as a component of cancer immunotherapy, each of these areas is under intensive investigation (p. 458, col. 1). Studies in a tumor model (38C13 murine lymphoma) indicate that CpG was just as effective as CFA at inducing an antigen-specific antibody response (p. 458, col. 2). Weiner teaches that "[Preliminary studies suggest CpG ODN can be effective in a variety of scenarios when used alone or in combination with other agents. Despite this promise we still do not understand the molecular mechanisms responsible for the immunostimulatory effects of CpG ODN. All CpG ODN are not alike, and more needs to be learned about the heterogeneous responses that occur based on host organism, cell subset, or CpG ODN sequence. Most importantly, we have not yet explored their clinical effects. Further work with CpG ODN in both the laboratory and the clinic is needed before we can know their true promise as investigational immunological and therapeutic agents." (p. 461, col. 1) Krieg et al (Pharmacol. & Therap. 84: 112-120, 1999) teach that CpG has NK-stimulating properties and suggest that it can be used in immunotherapy of tumors, yet Krieg et al also indicate that many or even most types of tumors are relatively resistant to NK-mediated lysis (p. 117, col. 2). Ballas et al (J. Immunol. 167: 4878-4886, 2001) teach that the selection of optimal CpG ODN for cancer immunotherapy depends upon a careful analysis of the cellular specificities of various CpG motifs and an understanding of the cellular mechanisms responsible for the anti-tumor activity in a particular tumor (abstract). Ballas et al teach that a single CpG ODN cannot be used to treat all cancers and tumors. Although several CpG ODN were active as sole immunotherapeutic agents in two tumor models, different motifs were optimal' in each model. CpG ODN 1585 was optimal against B16

melanoma and its effects were dependent on NK cells. CpG ODN 1826 was optimal in a lymphoma model and its effects appeared to require NK (early) and T cells (late). These results illustrate that the potent distinct CpG motifs can be custom-tailored for each desired immune effect (p. 4878, col. 2; see also p. 4885, col. 1). Agrawal et al (Trends in Molecular Medicine 813: 114-120, 2002) also teaches that different effects are observed with different CpG ODNs.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification provides guidance regarding the synthesis of the oligonucleotides (Example 1). The immunomers used in the examples are Immunomers 4, 5 and 6. Immunomer 6 has two accessible 5' ends, Immunomer 5 has no accessible 5' end and Immunomer 4 has a single accessible 5' end. Immunomer 6 provides greater splenocyte proliferation (*in vitro* assay) than Immunomers 4 and 5, and Immunomer 6 yielded greater immunostimulatory effects (*in vivo*) than Immunomers 4 and 5 (pgs 42-43). Other examples include *in vitro* assays on cytokine analysis, effect of chain length via *in vitro* assays, immunomer structure and activity, effects of linkers, as well as other *in vitro* assays (see examples in specification).

As stated above, the specification provides one *in vivo* example using mice to determine immunostimulatory activity via splenomegaly assays (Example 3). However, the specification does not provide any enablement for the *in vivo* use (animal or human) of the immunomers and their compositions in the treatment of the many disorders and diseases set forth in the specification. There is a lack of data and examples which adequately represent the scope of the claims as written.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

In view of the fact that similar extensive work has not been established for how these immunomers (at least two oligonucleotides linked together by a non-nucleotidic linker) would function in the many different treatments as proposed by Applicants, there would be undue experimentation for a person of skill in the art at the time the invention was made to practice the claimed invention. Although there is much known and defined about the CpG motif and its effective, the art still teaches that each CpG ODN behaves differently, different effects are observed with different CpG ODNs. Applicant's specification does not set forth any

enablement using the immunomers in a pharmaceutical composition (alone or with a cancer antigen) in a cancer treatment or any other antigen to treat viral or bacterial infections, autoimmune disorders, etc. There would be undue experimentation required to practice the use of the claimed compositions with a reasonable expectation of success that the claimed immunomer composition would be successful in treating any of the diseases and disorders proffered by Applicants, absent a specific and detailed description in applicant's specification of how to effectively use the claimed immunomer compositions and absent working examples providing evidence which is reasonably predictive of the use of the claimed composition for use in treating diseases and disorders.

Further, it is noted that a when a composition claim is limited by a particular use, enablement of that claim should be evaluated based on that use. In this case, the specification must teach enablement of a pharmaceutical use since the claim recites a pharmaceutical composition. According to Steadman's Medical Dictionary (24th Edition, 1982), "pharmaceutical" means "relating to pharmacy or to pharmaceutics". In the same dictionary, "pharmacy" is defined as: 1. The practice of preparing and dispensing drugs. 2. A drugstore. **Clinical p.,** a branch of p. practice that emphasizes the therapeutic use of drugs rather than the preparation and dispensing of drugs. Thus, broadly speaking, "a pharmaceutical use" would be one wherein something is being used as a "drug". Further, Steadman's Medical Dictionary (24th Edition, 1982) defines "drug" as "A therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man and animal." Likewise, Ansel et al (Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Edition), says "A drug is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or in other animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body." Considering all of this, a good definition for "a pharmaceutical use" would be any use, other than as food, wherein a substance is used on or in the body to prevent, diagnose, alleviate, treat, or cure a disease in humans or animals. The following are examples of "pharmaceutical uses": administering vitamin supplements (preventing disease); using labeled antibodies for *in vivo* imaging (diagnosing disease); administering a substance to alleviate a symptom of a disease (alleviating or treating disease); and administering an antibiotic (curing bacterial infection).

To enable a pharmaceutical use for a substance, the specification must teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment, or cure a disease in the animal to which the substance is administered. In the current situation the pharmaceutical composition (comprising Immunomer 6) administered to mice resulted in greater splenocyte proliferation. Immunomer 6 has an immunostimulatory effect. However, this does not indicate any prevention, diagnosis, alleviation, treatment or cure of any of the recited diseases and conditions in an animal to which the pharmaceutical composition (comprising immunomers) is administered. The specification describes a pharmaceutical use for the claimed pharmaceutical composition (see pg 14). However, the specification must enable a pharmaceutical use. In this case, while there are several pharmaceutical uses, the facts tell us that such a use is not enabled. Furthermore, administering immunomers to mice to produces greater splenocyte proliferation does not provide enablement for the claim because using the compound merely to produce antibodies for collection and subsequent use is not a pharmaceutical use. The pharmaceutical use must occur within the animal to which the compound/immunomers administered for the prevention, diagnosis, alleviation, treatment, or cure of disease.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. The specification shows how to make the claimed immunomers, however the specification is not enabled for the scope of the immunomers with regard to how to use. As previously set forth not all of these immunomers have an immunostimulatory effect.

Note, such a rejection as it pertains to pharmaceutical use could be overcome by deleting the word "pharmaceutical" from the claim. It is noted that when no use is recited in a claim, any enabled use will suffice.

Conclusion

13. No claims are allowed. The claims are free of the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036.

The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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PRIMARY EXAMINER